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Measuring Well-Being in Clozapine-Treated Schizophrenia Patients: the significance of positive symptoms

Running title: Well-being in clozapine-treated schizophrenia

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Abstract

Objectives

Well-being perception is seldom explored in schizophrenia patients. Recurrent limitations, such as the questionable applicability of gold standard defintions of health and well-being, and fewer tools available to assess well-being, are pronounced in this subpopulation. This cross-sectional study sought to explore potential clinical factors that may predict subjective well-being scores in chronic schizophrenia patients (N=142) receiving clozapine treatment,

Methods

The Short Warwick-Edinburgh Mental Well-being Scale (SWEMWBS) was used to measure well-being. We correlated SWEMWBS scores and 27 clinically recognised factors, spanning socio-demographics, symptom severity scores, physical health diagnosis, clozapine side effects, habits and prescribed medication. Factors with a $p<0.2$ correlation were included as a predictors in a linear regression model.

Results

Ten factors were included in the linear regression model, however only positive symptom severity was a significant predictor of SWEMWBS score ($p<0.003$).

Conclusions

The results suggest that the SWEMWBS is an efficient tool for measuring wellbeing in patients with chronic schizophrenia. We suggest that greater levels of clinical attention given to positive symptoms compared with other symptoms and aspects of well-being, during biomedical treatment for chronic schizophrenia, may partially explain the finding that only positive symptoms significantly predicted patient perceptions of low well-being.

Key words

Schizophrenia; Well-being; Subjective experience; Treatment-resistant schizophrenia; Clozapine

Highlights

- Lower levels of well-being in schizophrenia need to be clinically accounted for
- Positive symptoms in chronic schizophrenia influence eudemonic well-being
- Both quantitative and qualitative research may improve clinical comprehension

1. Introduction

Well-being and health perception is seldom measured in schizophrenia patients, and it is conceivable that subjective well-being and health perception amongst schizophrenia patients presents a different context from that of general population models. Concepts of health, mental health and quality of life are typically situated within the World Health Organisation (WHO) definition of health as ‘complete physical, mental and social well-being' [1], and mental health as ‘a state of well-being in which the individual realizes his or her own abilities’ [2]. Characteristics of schizophrenia, such as reality distortion, restricted emotional life, impaired cognition and lack of personal insight [3], along with antipsychotic side effects such as weight gain, sedation, hyper-salivation, or parkinsonism [4, 5], may impinge on well-being conceptions such that gold standard definitions and clinical perceptions of wellbeing are incongruent. By investigating how patients’ perceptions pertain to gold standard well-being definitions, we may better understand patient engagement in health care [6], and better assist patients to achieve full recovery.

It is suggested that ‘health related quality of life’ is significantly lower in persons with schizophrenia than in general population comparisons [7]. Previous research has indicated that both physical and mental aspects of health, measured separately, correlate with subjective quality of life amongst people with serious mental illness [8, 9]. Eudemonic, rather than hedonic, aspects of well-being have been positively

linked to biological and psychological resilience to stressors and negative health outcomes [10]. Further, lived experience and social situation contribute to subjective perceptions of health and well-being in schizophrenia [8, 11]. The influence of clinical perceptions and treatment focus, such as symptom alleviation, as part of an individual's experience and context, should therefore be critical to understanding subjective well-being in the course of schizophrenia treatment.

Clinical ideals of well-being tend to concern symptomatology, while instruments to measure subjective well-being concern either symptom severity or general life satisfaction, with mixed evidence of concordance with patient perceptions. The extent to which a patients' perceptions of well-being is consistent with clinical perceptions of well-being is unclear [12]. Recent studies suggest that perceptions of high quality of life cannot be predicted by levels of cognitive function amongst people with schizophrenia [8, 13]. Different studies have attributed patient well-being to different symptom domains in schizophrenia, including severity of negative symptoms [14, 15], positive symptoms [11] or depressive symptoms [15-17]. However, there is limited replication of these studies and also a lack of consistency in measurement tools and treatment variables used.

When subjective instruments are framed around general life satisfaction rather than symptom severity, both positive and depressive symptoms are implicated. Positive symptoms have been found to be predictive of lower subjective life satisfaction if queried on its' own terms using more general sub-scales, whereas quality of life based on symptom deficits is predominantly linked with negative symptom alleviation [11]. Yet if subjectively rated life satisfaction is framed as a singular query and compared with a wide range of clinical variables in a large cohort of chronic schizophrenia patients, depressive symptoms have been found to be the most, albeit moderate, predictive clinical factor [17]. Moreover, the expanse of items on subjective wellbeing scales, the range of clinical variables including treatment type tested, and consideration for illness chronicity may yield different study outcomes.

To take a particular treatment case study, the clinical determinants of well-being in clozapine treatment for schizophrenia may have implications for the treatment of schizophrenia more generally. Clozapine prevails as the gold standard treatment for schizophrenia because of its efficacy in alleviating positive symptoms and, to some extent, negative symptoms [18]. Compared with other second-generation antipsychotic drugs, clozapine treatment has been associated with higher levels of general wellbeing in schizophrenia [19], despite potentially debilitating side effects [20]. However, it is not known whether positive symptom alleviation in the context of other clinical concerns pertaining to clozapine treatment impact eudemonic aspects of wellbeing, otherwise linked to improved general health [10]. It is pertinent to understand the relevance of clinical assessments in terms of what constitutes patient well-being under schizophrenia treatment regimes like clozapine that may compromise other areas of health and lifestyle.

In order to disentangle what particular factors may predict patients' sense of well-being in clozapine treatment for schizophrenia, it might be useful to rate 'mental' well-being on its own terms to then be compared with other variables such as treatment, social situation and symptomology compared to other instruments validated to measure holistic functioning amongst clozapine-treated schizophrenia patients [19]. The Warwick-Edinburgh Mental Well-being Scale was designed to measure affirmative aspects of mental well-being [21]. The Short Warwick-Edinburgh Mental Well-being Scale (SWEMWBS) enlists 7 eudemonic aspects of well-being and is more efficient in terms of patients' time and willingness to respond [22, 23]. While the SWEMWBS is validated for general population use [22, 23] and easy to use for both patient and clinicians, it has not been used in schizophrenia and this study might contribute to its applicability to this population.

This study is the first to investigate how eudemonic aspects of well-being compare with clinical perceptions of well-being guided by symptom severity in clozapine patients in particular. We investigated how patient's perception of well-being is influenced by a range of clinical factors in a relatively large cohort that we characterized as stable clozapine chronic schizophrenia patients. We hypothesized that symptom severity, physical health complications, antipsychotic side effects and demographic factors are all associated with well-being perception in stable chronic schizophrenia patients treated with clozapine.

2. Material and Methods

2.1 Design and Study Sample

Clinical assessments and subjective well-being assessments of clozapine treated patients were compiled from an electronic clinical database at the Cambridgeshire and Peterborough NHS Foundation Trust Clozapine Clinic, where all patients receive mandatory monthly blood monitoring (described below) and annual review by a consultant psychiatrist. Assessments were collected at the same point in time for each participant, between October 2012 and May 2015.

2.2 Electronic Records

The Clinical and Research Database for Persistent Schizophrenia is an ethically approved electronic database (13/EE/0121) containing two sets of data for the Clozapine Clinic service users: clinical data from consultations and research data from service users who are/have participating/participated in research studies. All data was de-identified, maintaining anonymity. Data from October 2012 to June 2015 were included in the analysis.

2.3 Inclusion/Exclusion criteria

The study only included stable chronic schizophrenia patients. Non-schizophrenia patients [24] and those with less than four years of continuous treatment with clozapine or who were clinically unstable (measured as changes of more than 10 points at the GAF scale in two years) were excluded from the final analysis.

2.4 Measures of Assessment

Assessments included were: review and confirmation of all prescribed medication (latest clozapine plasma levels results), current smoking habit (average number of cigarettes per day) and alcohol use (average number of alcohol units per week), assessment of physical exercise using the General Practitioner Physical Activity Questionnaire ("General Practice Physical Activity Questionnaire (GPPAQ) – Publication – GOV.UK" 2015) and clozapine common side effects specific assessment (hours of sleep per day, constipation, hypersalivation, obsessive symptoms, Type 2 Diabetes Mellitus -T2DM-, hypertension, hyperlipidaemia and obesity) and different symptoms rating scales for symptom severity assessment, such as Global Assessment of Functioning (GAF) [25, 26], the Clinical Global Impression-schizophrenia (CGI-SCH) [27] and the Short Warwick-Edinburgh Mental Well-being Scale (SWEMWBS) [22].

The GAF is a clinician rated scale of functioning (0-100) and has been validated for assessing symptom severity and social functioning among people with chronic schizophrenia rather than acute psychosis [28]. It is therefore an appropriate assessment tool for clozapine patients. The CGI-SCH [22] is a validated version of the CGI [29] specific for schizophrenia, rating symptom severity on a scale of 1-7 ('normal, not at all ill' (1); 'borderline mentally ill' (2); 'mildly ill' (3); 'moderately ill' (4); 'markedly ill' (5); 'severely ill' (6); 'among the most extremely ill patients' (7). Mildly ill (3) is generally considered to be the threshold for clinically relevant psychopathology. In regards to positive symptom alleviation, the CGI-SCH includes four domains (positive, negative, depressive and cognitive symptoms) and an overall score (which mimics the CGI) [27, 30].

Our study used the SWEMWBS [22], which asks participants to nominate how often ('none of the time'; 'rarely'; 'some of the time'; 'often'; 'all of the time') the following statements have applied to them in the last two weeks: 1) 'I've been feeling optimistic about the future'; 2) 'I've been feeling useful'; 3) 'I've been feeling relaxed'; 4) 'I've been dealing with problems well' 5) 'I've been thinking clearly'; 6) 'I've been feeling close to other people'; 7) 'I've been able to make up my mind about things'. An internal construct validity study [21] was used to correct final scores, which ranged from 7 to 35; a high score reflecting a high level of well-being perception.

Pharmacological treatment was accounted for in terms of whether participants were taking only clozapine ('monotherapy'), or clozapine combined with other psychoactive pharmaceuticals (See **table 1).**

2.5 Statistical analysis

Clinical, self-rated and demographic variables were measured using descriptive statistics. The relationship between variables was determined using Pearson's correlation. Chi-square was used for categorical comparisons.

The following research question was interrogated:
Which clinically recognized factors correlate with patient well-being perception? We used a 2 stages approach [31] to answer this question. First, among the 27 factors aforementioned (see **table 1**), we determined those factors that were associated with well-being, aiming to be over inclusive and setting a threshold of $p<0.2$. A multiple regression model was built in a stepwise procedure retaining candidate variables with the previously established threshold and using the SWEMWBS mean score as dependent variable. We selected the option backward elimination (BE), which involves starting with all candidate variables, testing the deletion of each variable using a chosen model comparison criterion, deleting the variable that improves the model the most by being deleted, and repeating this process until no further improvement is possible [31].

For all analyses, the level of statistical significance was defined as $p<0.05$ (two-tailed). Statistical analysis was carried out using the SPSS programme (version 19.0).

3. Results

Of the 175 subjects included in the database, 15 subjects were excluded from the initial sample due to differential diagnosis (i.e. schizoaffective disorder, off label use for borderline personality disorder) and 27 due to not having clinical and clozapine treatment stability, as defined by the inclusion criteria. The final sample included 145 subjects. Demographic, baseline clinical and treatment characteristics of the subjects are presented in **Table 2**.

The mean well-being score and GAF was 21.64 (SD=3.89; See **Figure 1**) and 68.82 (SD=15.09), respectively.

The ten main factors associated with well-being with a $p<0.2$, which we included in the regression model, are shown in **Appendix A**. Backward multiple regression revealed that positive symptoms severity (CGI-Positive) significantly predicted SWEMWBS score ($p<0.001$). The SWEMWBS score was not significantly associated with any other symptom severity scores or clinical factors such as type of treatment or additional treatment for side effects of clozapine ($p>0.05$). The overall model is statistically significant ($F(3, 122)= 6.02$, $p<.001$) and accounts for 14.5% of the variance ($R= 0.381$, $R^2=0.145$) (see **Table** 3 for the full model).

4. Discussion

This study supports that the SWEMWBS is an efficient tool for assessing subjective well-being in clozapine treatment for schizophrenia. We found that only positive symptoms were a predictor of low subjective well-being amongst this population of stable patients. In light of previous quantitative and qualitative research, this finding should be contextualized in terms of how clinical attention to various aspects of symptomology and treatment might shape patients' own perceptions of health and well-being.

Firstly, the mean SWEMWBS (21.64) for our chronic schizophrenia patient sample was lower than that of a general population sample (23.61; obtained through personal communication with the authors of the SWEMWBS and the SWEMBWS online resource based the 2011 Health Survey for England [32, 33]). This finding is consistent with previous research [7], emphasizing a need to improve eudemonic well-being in treatment for chronic schizophrenia. The normal distribution suggests that the SWEMWBS is a useful tool for measuring subjective well-being in patients with chronic schizophrenia.

The finding that only one type of symptom alleviation and no lifestyle factors correlated with subjective well-being in this study deserves careful consideration. Contrary to our hypothesis, we found that only positive symptoms may be a predisposing factor for low subjective well-being. No associations were

found between other variables such as negative and depressive symptoms, the type of treatment, the presence of side effects due to clozapine, alcohol and tobacco consumption or other demographical variables. The relationship between positive symptoms and subjective general well-being supports the findings of another study [11]. However, our study provides the first example of a statistical relationship between positive symptoms and, specifically, eudemonic aspects of well-being. Other studies utilizing more extensive tools in terms of time and range of well-being factors have found depressive symptoms to be predictive of subjective well-being [16, 34, 35], albeit these studies included no stable patients and smaller sample sizes.

As our study separated out other variables that might predict eudemonic well-being, our finding that only positive symptoms correlated with SWEMWBS score, supports clinical assumptions that psychotic symptoms impact an individuals' sense of capability. This finding also supports the positive benefit-to-risk ratio pertaining to clozapine treatment, whereby additional health risks are clinically understood to be secondary to the potential for positive symptom alleviation [18]. This is particularly important as our sample included stable patients, in which psychosis severity seems to be the main driver of distress. Interestingly, this finding supports an American ethnographic study that found patient interpretations of 'recovery' to mostly concern psychotic symptom alleviation in spite of extensive reporting of medication-associated side-effects [36]. As qualitative research findings assert, whether or not patients themselves de-emphasise the illness or medication effects in their conceptions of well-being is critical to understanding the impact of clinical judgments on a person's subjectivity [36, 37]. As the SWEMWBS does not make mention of symptoms but rather perceptions of self efficacy and potential, our study suggests that the presence of psychotic symptoms may indeed contribute to what anthropologists term 'social defeat' in schizophrenia, in a Western biomedical context [38]. Regardless of whether the negative experience of psychotic symptoms may be culturally confined [39, 40], the biomedical priority of alleviating psychosis remains important for improving an individuals' sense of capability given the Western social context. However, it should also be noted that this finding might reflect the emphasis on positive symptoms inherent to antipsychotic treatment regimens. Moreover, the bivariate correlation between positive symptom severity and well-being perception was not strong, suggesting that there should be more factors associated with well-being that deserve further investigation, possibly incorporating qualitative research into this specific population.

Arguably, the influence of negative symptoms, depressive symptoms and lifestyle behaviours on an individuals' sense of well-being, health and quality of life may gain more traction as important aspects if given more clinical attention, especially in regards to patients who present with lack of insight into their primary health condition. As our study did not include measures of level of insight, our finding that positive symptoms predict low levels of well-being may be confounded by the possibility that concordant clozapine patients, subscribing to an end-of-the-line regular monitoring regime, are less likely to lack insight into a need for antipsychotic medication. Alternatively, the persistence of negative and depressive symptoms along with lifestyle behaviours, in spite of subjective well-being levels, may point to greater issues of patient disconnection from - and subsequently poor insight into - vulnerabilities associated with physical, mental, and social well-being. Given that depressive symptoms influence subjective well-being amongst clozapine patients if the measurement is framed around a variety of well-being aspects [16], further research is needed to investigate the interplay between clinical symptomology and patient perceptions.

The interpretation of the results should be considered in light of some limitations. Firstly, our study is cross-sectional and it is not possible to establish a true cause and effect relationship between psychotic symptoms and subjective well-being [41]. A longitudinal study would establish consistency of results over time. Secondly, because this study is naturalistic and without randomization, clinician bias might have been present in the symptomatology rating scores, although symptom severity scores were done immediately before patients completed the well-being scale. Thirdly, socioeconomic variables could be controlled for in future studies. Finally, this study did not employ a scale to assess other aspects of quality of life, to compare against eudemonic framing of well-being, nor were we able to include a measurement for patient insight. Future studies might also include observed-rated scales in addition to self-reporting in order to capture the correlates of subjective well-being, quality of life and functional outcome.

Additionally, qualitative data may compliment efforts to understand how other aspects of symptomology and treatment, not found to be significant in so far as predicting SWEMWBS score, may impact quality of life in chronic schizophrenia.

In conclusion, the results of our study suggest that positive symptoms are predictive of low well-being perception in chronic schizophrenia patients receiving clozapine treatment. Given the current situation of questionable health-related quality of life and well-being among people with chronic schizophrenia on long-term treatment regimes, it is critical to utilize efficient subjective measures of well-being such as the SWEMWBS, and to attend to how clinical perceptions of patients' general functioning in schizophrenia reflect patients' views. Moreover, the extent to which perceived functioning and well-being are associated with longer-term outcomes such as relapse, co-morbidities, and treatment concordance requires ongoing quantitative and qualitative research efforts to identify which domains and measures of health-related quality of life are most germane to treating schizophrenia.

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Declaration of Interest

Ms Brown and Ms Mezquida declare no conflicts of interest. Dr. Fernandez-Egea has received unrestricted research funding from Genus Pharmaceuticals, and consultancy fees from Roche/Genentech, however declares no bias given these funding affiliations.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Table 1. Measures of assessment and variables included in the study:

Demographical variables	Gender (male / female)	
	Age (years)	
	Age of FEP (years)	
	Smoking habit (average number of cigarettes per day)	
	Alcohol use (average number of alcohol units per week)	
Prescribed medication	Latest clozapine plasma levels results	
Physical activity	General Practitioner Physical Activity Questionnaire (GPPAQ)	
Clinical Assessment	CGI- Positive	
	CGI- Negative	
	CGI- Depressive	
	CGI- Cognitive	
	CGI- Overall	
	GAF	
	Corrected Short Warwick-Edinburgh Mental Well-being Scale (cSWEMWBS)	
Clozapine main side effects	Hypersalivation	
	Hours of sleep per day	
	Constipation	
	Obsessive symptoms	
	Hypertension	
	Overweight	
	Hyper-lipidaemia	
	Type 2 diabetes mellitus	
Pharmacological treatment	Monotherapy with clozapine	
	Clozapine combined with other drugs	Clozapine and Other antipsychotics
		Clozapine and Antidepressants
		Clozapine and Drugs for side effect symptoms (beta-blockers)
		Clozapine and Other medication

FEP: First-episode psychosis**; GAF:** Global Assessment of Functioning; **CGI:** Clinical Global Impression

Table 2. Demographical and clinical characteristics of the 142 stable chronic schizophrenia patients treated with clozapine. Figure represent mean and (standard deviation) except otherwise specified.

Gender (male / female)	115 / 26
Age (in years)	44.33 (9.67)
Age of onset (in years)	22.83 (6.85)
Tobacco use (%)	47.9%
Tobacco use (cigarettes/day)	18.07 (8.92)
Alcohol use (%)	41.1%
Alcohol units per week	11.14 (11.54)
Dose of clozapine (mg)	331.03 (141.01)
Clozapine Monotherapy (%)	39.0%
Well-being score	21.64 (3.89)
GAF score	68.82 (15.09)
CGI- Positive **CGI- Negative** **CGI- Depressive** **CGI- Cognitive** **CGI- Overall**	2.68 (1.58) 3.26 (1.47) 1.72 (0.99) 2.94 (1.19) 3.42 (1.34)

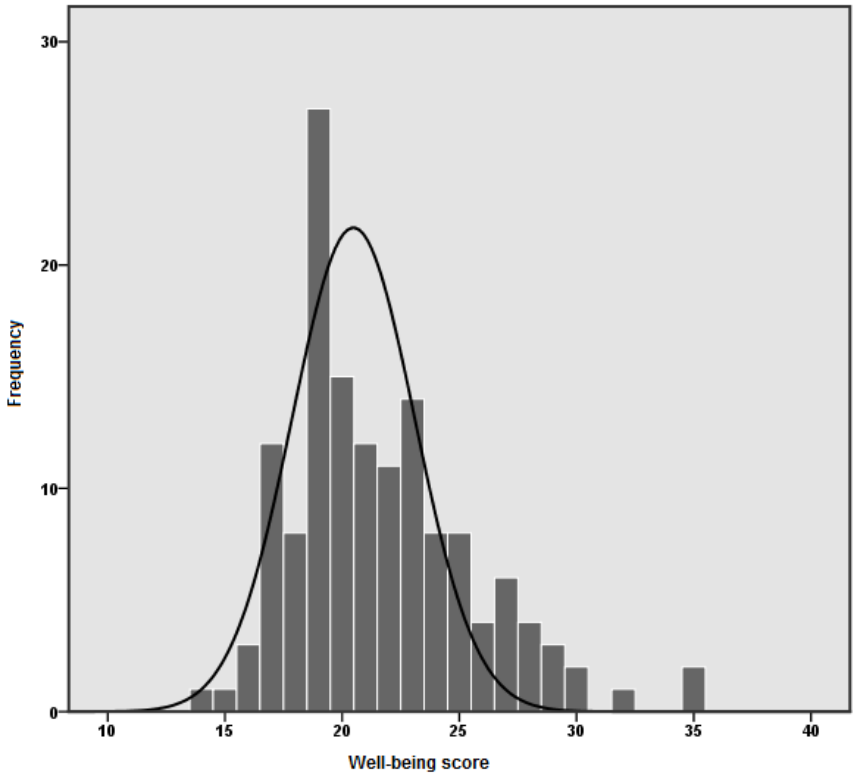
SD: standard deviation**; FEP:** First-episody psychosis**; GAF:** Global Assessment of Functioning; **CGI:** Clinical Global Impression

Table 3. Multiple regression model, with well-being score (from SWEMWBS) as the dependent variable.

Variables	B	Beta	t	Sig. p value	95.0% Confidence Interval for B	
					Lower Bound	Upper Bound
CGI- Positive	-.776	-.317	-3.780	**<.000**	-1.183	-.370
Overweight (SE)	-.651	-.144	-1.681	.095	-1.417	.115
Clozapine and antidepressants	-1.384	-.164	-1.923	.057	-2.808	.040

***P* value significant at p<0.05 is highlighted in bold,**
B-value=unstandardised coefficient, *β*-value=standardized coefficient for each determinant
The excluded determinants are not described in this table.
SE: Side Effect due to clozapine; **CGI:** Clinical Global Impression

Figure 1. Well-being mean scores in chronic schizophrenia patients.



Appendix A. Correlations of well-being with demographic and clinical variables in chronic schizophrenia patients.

Factors correlated with well-being	r	*p*
Age	.083	.327
Age of FEP	-.050	.554
Smoking amount	-.133	**0.016**
Alcohol units	.111	**0.171**
Latest Clozapine levels	-.056	.601
GPPAQ	.062	.471
CGI- Positive	-.310	**<0.000**
CGI- Negative	-.163	**0.060**
CGI- Depressive	-.235	**0.007**
CGI- Cognitive	-.094	.397
CGI- Overall	-.200	.017
GAF	.149	.077
Hypersalivation (SE)	-.147	**0.082**
Hours of sleep per day (SE)	-.020	.814
Constipation (SE)	-.079	.353
Obsessive symptoms (SE)	-.076	.418
Hypertension (SE)	.079	.409
Overweight (SE)	-.112	**0.189**
Hyper-lipidaemia (SE)	.045	.658
Type 2 diabetes mellitus (SE)	.050	.610
Monotherapy (with Clozapine)	.220	**0.009**
Clozapine + other antipsychotics	-.023	.784
Clozapine + antidepressants	.-196	**0.019**
Clozapine + drugs for SES	-.164	**0.051**
Clozapine + other medication	-.057	.502

Associations $p<0.2$ are indicated in bold.

SE: Side Effect due to clozapine, **CGI:** Clinical Global Impression, **GPPAQ:** General Practitioner Physical Activity Questionnaire, **GAF:** Global Assessment Functioning